REMARKS

Status of the Claims

Claims 86-96, 101-112 and 116-123 were pending, of which claims 91, 106 and 112 were deemed withdrawn. Claims 86-90, 92-96, 101-105, 107-111 and 116-123 were examined in this Office Action.

In the present amendment, all previously presented claims have been cancelled without prejudice, no claims are amended, and new claims 124-152 are introduced. Following entry of the present amendment, claims 124-152 are pending and presented for examination.

Amendments to the Claims

All of the previously pending claims have been cancelled without prejudice. New claims 124-152 have been submitted to further clarify the nature of the claimed invention. Support for claims 124-152 may be found in claims 1-85 as originally filed, as well as throughout the specification; for example, in Example 3; page 54, line 24, to page 55, line 9; page 31, lines 11-14; and page 12, lines 14-22. No new matter is added by these amendments.

Telephonic Interview

Applicants thank Examiner Steadman for a productive telephonic interview conducted on October 27, 2011, with Michael Heartlein, Randy Morin, Fangli Chen and Justin Huddleson.

During the interview, Applicants presented to the Examiner a proposed new claim set that is intended to better capture the claimed invention and to simplify claim language. The Examiner agreed that the proposed new claims are clear and suggested that Applicants recite "isolated" in the context of a sulfatase-producing cell for further clarification. The Examiner and Applicants' representative discussed the language "wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme." Applicants'

representative explained to the Examiner that this language illustrates a result of the claim invention but is not intended to limit the scope of the claims.

During the interview, Applicants also presented arguments for nonobviousness of the claimed invention. In particular, Applicants' representative pointed out that, prior to the present invention, no one could have thought to coexpress a sulfatase and a FGE protein in order to increase the ratio of the active sulfatase to total sulfatase produced in a cell because the FGE protein was not purified and the gene was not cloned. Co-inventor Dr. Michael Heartlein presented to the Examiner the history, background and technical difficulties surrounding the purification of the FGE protein and the unexpected result rendered by coexpressing a sulfatase and an FGE enzyme in a cell. Applicants' representative offered to submit a declaration to include the facts and statements Dr. Heartlein presented based on his personal knowledge if it would be helpful. Examiner Steadman indicated that such a declaration may be helpful but not necessary.

Applicants thank Examiner Steadman for a productive interview. Applicants have incorporated the Examiner's suggestions in this response.

Claim Objections

Claims 86 and 92-93 were objected to as being in improper claim form. Claims 86 and 92-93 have been cancelled by the present amendment; thus, all objections with respect to these claims are moot.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 86-90, 92-96, 101-105, 107-111, and 116-123 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 86-90, 92-96, 101-105, 107-111 and 116-123 have been cancelled by the present amendment; thus, all rejections under 35 U.S.C. § 112, second paragraph with respect to these claims are moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 86-90, 93-96, 101-105, 108-111, and 116-123 stand rejected under 35

U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims.

Claims 86-90, 93-96, 101-105, 108-111 and 116-123 have been cancelled by the present amendment; thus, all rejections under 35 U.S.C. § 112, first paragraph with respect to these claims are moot.

Rejections under 35 U.S.C. § 102/103(a) and 103

Claims 86-90, 93-96, 101-105, 108-111, and 116-123 stand rejected under 35 U.S.C. § 102(b) as being anticipated or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Rommerskirch et al (Proc. Natl. Acad. Sci. USA, 89:2561-2565, 1992) ("Rommerskirch") as evidenced by Eto et al. (Eur. J. Pediatr. 135:85-89, 1980) ("Eto") and Dierks et al. (Cell 113:435-444, 2003) ("Dierks"). Claims 101-105, 107, 119 and 123 are rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Pat. No. 7,083,793 to Fraser et al. ("Fraser") as evidenced by Landgrebe et al. (Gene 316:47-56, 2003) ("Landgrebe"), Plasmid Vectors (obtained from www.mfa.od.ua/page275.htm) and Dierks. Claims 86-90, 92, 117, and 121 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Pat. No. 7,368,531 to Rosen et al. ("Rosen") in view of Fraser as evidenced by Landgrebe, Plasmid Vectors and Dierks.

Claims 86-90, 93-96, 101-105, 108-111, and 116-123 have been cancelled by the present amendment; thus, all rejections with respect to these claims are moot.

New claims 124-152

For the sake of completeness and in the interest of advancing prosecution, Applicants provide the following arguments to distinguish over the cited references to the extent they are applicable to new claims 124-152.

Applicants respectfully submit that new claims 124-152 are novel and not obvious over the cited references, alone or in combination.

New independent claim 124 recites:

> 124. An isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:
>
> (i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

New independent claim 141 recites:

141. An isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the Formylglycine Generating Enzyme.

Thus, the claimed invention is directed to an isolated sulfatase-producing cell containing a sulfatase and an over-expressed FGE (claim 124) or an over-expressed sulfatase and a FGE (claim 141), wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the FGE or over-expressed FGE.

None of the cited references teach or suggest the claimed invention. Specifically, Rosen and Fraser are irrelevant to the subject matter claimed in new claims 124-152. Dierks and Landgrebe are not prior art since they both published in 2003, later than the effective filing date of the present application. Numaguchi simply teaches that impaired degradation of labeled sulfated compounds can be demonstrated *in vivo*. Numaguchi, Title and Abstract. The only reference discusses post-translational modification to all sulfatases is Rommerskirch.

Rommerskirch teaches that "the mutation in MSD[1] severely decreases the capacity of a co- or post-translational process that renders sulfatases enzymatically active or prevents their premature inactivation." Rommerskirch, Abstract. Specifically,

[1] MSD stands for Multiple Sulfatase Deficiency.

Rommerskirch expressed three sulfatases in MSD fibroblasts by retroviral gene transfer. All three sulfatases have severely diminished catalytic activity suggesting that the basic defect in MSD affects a post-translational process that controls the catalytic properties of sulfatases. Rommerskirch, Abstract and Discussion. However, Rommerskirch does not teach or suggest that the Formylglycine Generating Enzyme caused the defect that affects the post-translational modification. In fact, Rommerskirch clearly stated "[t]he nature of the modification that renders ASA polypeptides active or prevents their inactivation is ***not clear***." Rommerskirch, Discussion, page 2565, left column, the last paragraph, emphasis added.

In fact, the nature of the modification was unknown for many years after Rommerskirch was published. As Dr. Heartlein discussed during the interview of October 27, 2011, it was unclear to him and other scientists in the field at the time if this post-translational modification process was controlled by a machinery of molecules, a complex of molecules or a single molecule. Indeed, it took over six years of hard work for the present inventors and their co-workers to eventually purify the protein associated with this post-translational modification process, the Formylglycine Generating Enzyme, in December of 2002. This work co-authored by Thomas Dierks and Kurt von Figura (both are co-inventors of the present application) was published in the leading scientific journal *Cell* in 2003, 11 years after the publication of Rommerskirch in 1992. These facts clearly confirmed that it simply *cannot* be obvious for one of skill in the art to purify the FGE protein in view of the teachings in Rommerskirch.

The claimed invention is based on the discovery of the molecule or molecules responsible for the post-translational modification of sulfatases. This discovery required the isolation of those molecules or that molecule. As discussed above, the isolation of that molecule - FGE protein - was not trivial. Co-inventor Dr. Thomas Dierks described the process in two declarations submitted in the European counterpart application (European Patent Application No. 04709824.9-2406). The European examiner has recently allowed the European application in part based on these declarations. Copies of these declarations are submitted herewith as Appendices A and B for the Examiner's reference.

In addition, as Dr. Heartlein discussed during the interview, it was completely

unexpected to him and his co-inventors that coexpression of FGE and a variety of sulfatases in cells increases the activity of the sulfatases produced by the cells, as embodied in Applicants' claims. Indeed, Applicants' claimed invention has solved a long-standing problem that existed with manufacturing sulfatases as drug products for the treatment of various sulfatase deficiencies. As Dr. Heartlein discussed during the interview, prior to the present invention, it was known that over-expression of sulfatases in cultured cells yielded a reduced percentage of active sulfatases in the total enzymes produced by the cultured cells. It has been successfully demonstrated that cells coexpressing FGE and sulfatases as claimed in Applicants' new claims can produce sulfatases with increased percentage of the active sulfatases as compared to those sulfatases produced without FGE. Indeed, Applicants' claimed cells allowed pharmaceutical companies like Shire, the assignee of the present application, to be able to manufacture drug products for treating various sulfatase deficiency diseases more efficiently and to improve the quality of the drug product itself. This invention has been licensed to another biotech company who is using Applicants' claimed invention to manufacture their drug product for treating a sulfatase deficiency disease. Therefore, these facts further confirm that Applicants' claimed invention cannot be obvious and provide unexpected benefits to the companies that produce sulfatase-based drugs and to the patients who are suffering from sulfatase deficiency diseases.

For at least all of these reasons, Applicants submit new claims 124-152 are novel and nonobvious over the teachings of the prior art.

CONCLUSION

In view of the amendments and the arguments above, Applicants believe that all rejections have been overcome and the pending claims are in condition for allowance. Applicants thank Examiner Steadman for his time and consideration of new claims 124-153 submitted herewith. If any issues remain outstanding following consideration of the present amendment, or the examiner would like to discuss the invention further, Examiner Steadman is invited to call the undersigned. If any additional fee is required other than that already noted, please charge any deficiency in fees or credit any overpayments to Deposit Account No. 03-1721, referencing Attorney's Docket Number **2006685-0065**.

Respectfully submitted,

/Fangli Chen/
Fangli Chen, PhD, JD
Registration No.: 51,551

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CHOATE, HALL & STEWART LLP
Patent Group
Two International Place
Boston, MA 02110
Tel: 617-248-5000
Fax: 617-502-5002
patentdocket@choate.com